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Lessons/successes in fighting atherosclerosis using gene therapy of cytokines and their downstream genes in mice

Cardiovascular disease (CVD) remains one of the biggest killers of the aged. As CVD is a long term disease, usually taking decades to develop, therapeutic gene therapy (GT) could be a well matched treatment. Adeno-associated virus (AAV) gene delivery lasts years and is safe. This leaves the identification of appropriate genes for treating CVD as a main block for clinical CVD GT. Over the last few years we have been utilizing AAV-based GT to deliver anti-inflammatory cytokines, specifically interleukin 10 (IL-10) and transforming growth factor beta 1 (TGFbeta1). We have utilized the low density lipoprotein receptor knockout mouse (LDLR KO) on high cholesterol diet (HCD) to study these GTs as this model is believed the best in mimicking atherogenesis in humans on a high fat Western diet. As both TGFbeta1 and IL-10 are known to give complications when used clinically and/or in animal models, we have extended our search to the downstream signal transduction genes of IL-10 and TGFbeta 1. Such genes might be intracellular substitutes for these somewhat hazardous systemic cytokines. Obviously, the GT of intracellular proteins is a dramatically different approach to that of GT of secreted proteins. STAT3 was investigated as a substitute for IL-10, and while it did display therapeutic efficacy, its efficacy trended weaker than IL-10. Moreover, IL-10 plus STAT3 dual gene delivery gave no advantage over either gene delivered alone. Yet, STAT3 GT may still be a viable treatment as it might give fewer adverse reactions than IL-10. Moving on, SMAD3 GT was investigated as a substitute for TGFbeta1, and it also did display therapeutic efficacy. Additionally, and fortuitously, SMAD3 gene delivery did not display the well known attribute of promoting fibrosis, as is well known for TGFbeta1. Thus, SMAD3 may represent a successful GT approach with a significant advantage over its parent cytokine. We have also accumulated additional data on other cytokines/genes and their therapeutic value. Here, now, we are at a crossroads in anti-CVD GT. All our GT studies have been done on limiting atherogenesis, limiting the development of CVD, using one mouse model (LDLR KO mice on HCD). While our studies give us valuable information and are relevant, they may not represent the most accurate model for analyzing therapeutic GT strategies against established human CVD. Additional approaches and models, such as the use of different mouse models, disease-specific or cell-specific transcriptional promoters, and dual gene GT will be discussed

Biography

Paul Hermonat received his Ph.D. from the University of Florida in 1984. There he mutationally mapped the genes of AAV and carried out the first AAV-based gene transfer experiments. Now at the University of Arkansas for Medical Sciences, he has 141 publications and has helped lay the foundation of knowledge on AAV molecular biology and its use in gene therapy. Presently he studies AAV-based gene therapy for treating cardiovascular disease and cancer, and studies the use of helper genes for AAV production.

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